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(54) Title: CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING TRAMADOL HYDROCHLORIDE AND METHOD FOR ITS PREPARATION

(57) Abstract: The invention solves a controlled release pharmaceutical composition containing tramadol hydrochloride, characterized in that it contains 100 to 200 mg of the active ingredient in admixture with micronized esters of glycerol with higher fatty acids, alkali salts of phosphoric acid, non-ionic vinylpyrrolidone polymers, substances from the group of salts of higher fatty acids with alkaline earth metals and silicon oxides and a method for the preparation of this composition.

Controlled release pharmaceutical composition containing tramadol hydrochloride and method for its preparation

Technical Field

The invention belongs to the pharmaceutical field, it relates to the composition and the method of preparing of an oral therapeutic preparation in the form of controlled release tablets containing the active ingredient tramadol hydrochloride.

Background art

Tramadol hydrochloride containing therapeutic compositions in the form of controlled release tablets are described in SK patent No. 280496, according to which a formulation is prepared by melting a mixture of the drug and a hydrophobic or hydrophilic carrier in high performance homogenization devices with heating and cooling facilities. The molten, homogenized mixture is cooled down; particle size of the agglomerates is adjusted while undercooling the mixture in order to obtain desirable physical parameters for mechanic dividing and adjustment of the particle size for further processing.

As described in SK patent No. 280496, the meltable carriers include, e.g., waxes, hydrogenated vegetable oils and higher fatty acid esters with glycerol.

Document EP 0 624 366 A1 describes a formulation containing 50-800 mg tramadol, i.e. controlled release tablets, which are produced in a similar manner, or in the form of film coated spheres (agglomerates).

Drawbacks of the above preparation of solid formulations containing tramadol hydrochloride based on meltable hydrophobic or hydrophilic carrier include, in addition to energy and time consumption, necessity of special equipment. Another drawback is the surface finish of the tablets, which requires further special equipment and technology, and dividing of the tablets for dosage is not possible.

Disclosure of the Invention

This invention overcomes said drawbacks by a new, simpler, and low time and energy consuming method of preparing tablets containing 100 to 200 mg tramadol hydrochloride, not requiring special production equipment. Manufacture in the below described manner is practicable in pharmaceutical plants without need of one-purpose equipment.

The tablets made by the method of the invention fulfil the requirements for the release pattern and do not require any further finish by, e.g. film coating, which would influence the release rate.

The principle of the manufacture is a balanced mixture of the drug and the adjuvants, prepared by simple granulation, drying of the granulate, admixing further adjuvants facilitating the tableting process without need of further treatment of the compressed articles. Thus obtained tablets are physically and chemically stable, easily adjustable and ensure necessary optimal course of release of the active substance into the organism over the required time period even after possible dividing of the tablets.

The controlled release formulation according to this invention contains other adjuvants in addition to the active substance:

- a) Micronized esters of glycerol with higher fatty acids, preferably docosanoic acid glyceryl ester. They are of a particle size from 1 to 100 micrometers, preferably of a distribution the size of which is 1.5-60 micrometers in the range of 90 %. It has been determined experimentally in laboratory development that the most preferred content of the higher fatty acid glyceryl esters for the targeted drug release and optimal physical characteristics is from 10 to 53 % by weight, preferably, from 28 to 47 % by weight.
- b) Pharmaceutically applicable alkali salts of phosphoric acid, preferably calcium phosphate dihydrate, in amounts of from 20 to 41 % by weight, preferably from 24 to 39 % by weight.
- c) Non-ionic polymers of vinylpyrrolidone of relative molecular weight from 9000 to 90000, preferably 25000 to 30000, in amounts from 1.15 to 1.75 % by weight, preferably from 1.3 to 1.55 % by weight.

- d) Substances facilitating tableting process from the group of salts of higher fatty acids with alkaline earth metals, preferably magnesium stearate, in amounts of 1.5 to 3.2 % by weight, preferably from 1.8 to 2.8 % by weight, and silicon dioxide, preferably colloidal silica, in amounts of from 1 to 3 % by weight, preferably from 1.1 to 2.1 % by weight.

The manufacturing process of this invention consists in mixing the active substance in admixture with micronized higher fatty acid glycerol ester, preferably with glyceryl ester of docosanoic acid having a particle size of from 1 - 100 micrometers, preferably 1.5 - 60 micrometers, in an amount of from 10 % to 53 % by weight, preferably from 28 % to 47 % by weight, along with alkali salts of phosphoric acid, preferably calcium phosphate dihydrate, in an amount of from 20 % to 41 % by weight, preferably from 24 % to 39 % by weight. This mixture is moistened with a solution of a non-ionic vinylpyrrolidone polymer having a relative molecular weight of from 9,000 to 90,000, preferably from 25,000 to 30,000, in an amount of 1.15 to 1.75 % by weight, preferably from 1.3 to 1.55 % by weight, in a mixture of water and ethyl alcohol in an amount of from 30 % to 70 % by weight, preferably from 40 % to 60 % by weight.

The mixture is agitated while agglomerating. The obtained agglomerate is dried in a suitable manner either by fluidisation, in a chamber or in vacuo such that the mixture contain from 0.2-1.5 %, preferably from 0.5 to 1.2 % moisture.

The dried agglomerate is adjusted to a particle size that complies with the tableting process, and materials from the group of salts of higher fatty acids with alkaline earth metals, preferably magnesium stearate, in an amount of from 1.5 % to 3.2 % by weight, preferably from 1.8 % to 2.8 % by weight, and of silicon oxides, preferably colloidal silica, in an amount of from 1 % to 1.3 % by weight, preferably from 1.1 % to 2.1 % by weight, are added.

The mixture is agitated until homogeneous.

The mixture is tabletted, the break resistance of tablets ranging from 40 to 110 N, preferably from 50 to 90 N, for tablets of round, lenticular, oblong or other shapes.

Thus prepared tablets can be adjusted into commonly useful types of packages such as glass, plastics, metal packages and combinations thereof.

Examples

The following examples are intended to illustrate the invention without limiting its scope.

Example 1

a) pharmaceutical composition, containing in 1 tablet:

Tramadol hydrochloride	0.1000 g	21.74 %
Glyceryl ester of docosanoic acid	0.1700 g	36.96 %
Calcium phosphate dihydrate	0.1770 g	38.48 %
Polyvinylpyrrolidone	0.0070 g	1.52 %
Colloidal silica	0.0060 g	1.30 %

b) process for its preparation:

The active ingredient in admixture with micronized ester of glycerol with docosanoic acid having the particle size of from 1.5 – 60 micrometers in the amount of 36.96 % by weight is agitated in a suitable type of pharmaceutical granulator such as Diosna, along with calcium phosphate dihydrate in the amount of 38.48 % by weight, for 3 minutes.

Then the mixture is, under constant agitation, moistened with a solution of non-ionic vinylpyrrolidone polymer having the relative molecular weight of 25,000 in the amount of 1.52 % by weight in 60% ethanol.

The mixture is agitated, agglomerate thus being formed.

The prepared agglomerate is discharged from the granulator into the vessel of a fluidising drying device such as Glatt or Aeromatic and is dried at the temperature of fed air 55 °C until the temperature of the effluent air reaches 42 °C. At that point the product reaches residual moisture from 0.5 % to 1.2 %.

The particle size of the dried agglomerate is adjusted by passing through a screen having the mesh side of 1.25 mm on an oscillating device such as Frewitt. The adjusted agglomerate is transferred into a suitable type of pharmaceutical

homogenizer of the shape of cube or bulb, colloidal silica in the amount of 1.3% by weight is added and agitated until homogeneous. The obtained mixture is tabletted in rotary tableting machines of the type such as Manesty, Kilian, Fette etc. into round-shaped, biconvex tablets.

Tablet parameters:

Appearance	White to off-white, smooth, biconvex, round with dividing groove
Tablet diameter (mm)	11
Tablet height (mm)	4.75
Tablet average weight (g)	0.460
Tablet break resistance (N)	50-70

Dissolution of the active ingredient according to this invention as a function of time and its comparison with the product according to EP 0 624 366 A1:

Apparatus Pharmatest type PTWS 3:

Dissolution medium Water (Temperature 37 °, volume 600 ml, 100 rpm)	Time			
	Amount of released active ingredient, %			
	after 1 hour	after 3 hours	after 5 hours	after 8 hours
Tramadol 100-SL	38.90	63.46	77.09	90.44
Tramal ® Retard 100	35.73	65.80	81.75	93.75

Example 2

a) pharmaceutical composition, containing in 1 tablet:

Tramadol hydrochloride	0.1500 g	21.74 %
Glyceryl ester of docosanoic acid	0.2550 g	36.96 %
Calcium phosphate dihydrate	0.2655 g	38.48 %
Polyvinylpyrrolidone	0.0105 g	1.52 %
Colloidal silica	0.0090 g	1.30 %

b) process for its preparation:

The active ingredient in admixture with micronized ester of glycerol with docosanoic acid having the particle size of from 1.5 – 60 micrometers in the amount of 36.96 % by weight is agitated in a suitable type of pharmaceutical granulator such as Diosna, along with calcium phosphate dihydrate in the amount of 38.48 % by weight, for 3 minutes.

Then the mixture is, under constant agitation, moistened with a solution of non-ionic vinylpyrrolidone polymer having the relative molecular weight of 25,000 in the amount of 1.52 % by weight in 60% ethanol.

The mixture is agitated, agglomerate thus being formed.

The prepared agglomerate is discharged from the granulator into the vessel of a fluidising drying device such as Glatt or Aeromatic and is dried at the temperature of fed air 55 °C until the temperature of the effluent air reaches 42 °C. At that point the product reaches residual moisture from 0.5 % to 1.2 %.

The particle size of the dried agglomerate is adjusted by passing through a screen having the mesh side of 1.30 mm on an oscillating device such as Frewitt. The adjusted agglomerate is transferred into a suitable type of pharmaceutical homogenizer of the shape of cube or bulb, colloidal silica in the amount of 1.30% by weight is added and agitated until homogeneous. The obtained mixture is tableted in rotary tableting machines of the type such as Manesty, Kilian, Fette etc. into round-shaped, flat tablets with dividing groove.

Tablet parameters:

Appearance	Off-white, smooth, flat with dividing groove
Tablet diameter (mm)	12
Tablet height (mm)	4.2-4.5
Tablet average weight (g)	0.690
Tablet break resistance (N)	58-80

Dissolution of the active ingredient according to this invention as a function of time and its comparison with the product according to EP 0 624 366 A1:

Apparatus Pharmatest type PTWS 3:

Dissolution medium Water (Temperature 37 °, volume 600 ml, 100 rpm)	Time			
	Amount of released active ingredient, %			
	after 1 hour	after 3 hours	after 5 hours	after 8 hours
Tramadol 150-SL	40.32	67.12	80.24	95.09
Tramal ® Retard 150	34.74	65.2	83.36	95.58

Example 3

a) pharmaceutical composition, containing in 1 tablet:

Tramadol hydrochloride	0.1500 g	29.41 %
Glyceryl ester of docosanoic acid	0.1700 g	33.33 %
Calcium phosphate dihydrate	0.1770 g	34.71 %
Polyvinylpyrrolidone	0.0070 g	1.37 %
Colloidal silica	0.0060 g	1.18 %

b) process for its preparation:

The active ingredient in admixture with micronized ester of glycerol with docosanoic acid having the particle size of from 1.5 – 60 micrometers in the amount of 33.33 % by weight is agitated in a suitable type of pharmaceutical granulator such as Diosna, along with calcium phosphate dihydrate in the amount of 34.71 % by weight, for 3 minutes.

Then the mixture is, under constant agitation, moistened with a solution of non-ionic vinylpyrrolidone polymer having the relative molecular weight of 25,000 in the amount of 1.37 % by weight in 60% ethanol.

The mixture is agitated, agglomerate thus being formed.

The prepared agglomerate is discharged from the granulator into the vessel of a fluidising drying device such as Glatt or Aeromatic and is dried at the temperature of fed air 55 °C until the temperature of the effluent air reaches 42 °C. At that point the product reaches residual moisture from 0.5 % to 1.2 %.

The particle size of the dried agglomerate is adjusted by passing through a screen having the mesh side of 1.25 mm on an oscillating device such as Frewitt. The adjusted agglomerate is transferred into a suitable type of pharmaceutical

homogenizer of the shape of cube or bulb, colloidal silica in the amount of 1.18% by weight is added and agitated until homogeneous.

The obtained mixture is tableted in rotary tableting machines of the type such as Manesty, Kilian, Fette etc. into round-shaped, flat tablets with dividing groove.

Tablet parameters:

Appearance	Off-white, smooth, flat with dividing groove
Tablet diameter (mm)	11
Tablet height (mm)	4.41
Tablet average weight (g)	0.510
Tablet break resistance (N)	58-75

Dissolution of the active ingredient according to this invention as a function of time and its comparison with the product according to EP 0 624 366 A1.

Apparatus Pharmatest type PTWS 3:

Dissolution medium Water (Temperature 37 °, volume 600 ml, 100 rpm)	Time			
	Amount of released active ingredient, %			
	after 1 hour	after 3 hours	after 5 hours	after 8 hours
Tramadol 150-SL	42.30	68.7	82.90	95.15
Tramal ® Retard 150	34.74	65.2	83.36	95.58

Example 4

a) pharmaceutical composition, containing in 1 tablet:

Tramadol hydrochloride	0.2000 g	26.85 %
Glyceryl ester of docosanoic acid	0.3400 g	45.64 %
Calcium phosphate dihydrate	0.1800 g	24.16 %
Polyvinylpyrrolidone	0.0100 g	1.34 %
Magnesium stearate	0.0150 g	2.010 %

b) process for its preparation:

The active ingredient in admixture with micronized ester of glycerol with docosanoic acid having the particle size of from 1.5 – 60 micrometers in the amount of 45.64 % by weight is agitated in a suitable type of pharmaceutical granulator such as Diosna, along with calcium phosphate dihydrate in the amount of 24.16 % by weight, for 3 minutes.

Then the mixture is, under constant agitation, moistened with a solution of non-ionic vinylpyrrolidone polymer having the relative molecular weight of 25,000 in the amount of 1.34 % by weight in 60% ethanol.

The mixture is agitated, agglomerate thus being formed.

The prepared agglomerate is discharged from the granulator into the vessel of a fluidising drying device such as Glatt or Aeromatic and is dried at the temperature of fed air 55 °C until the temperature of the effluent air reaches 42 °C. At that point the product reaches residual moisture from 0.5 % to 1.2 %.

The particle size of the dried agglomerate is adjusted by passing through a screen having the mesh side of 1.25 mm on an oscillating device such as Frewitt. The adjusted agglomerate is transferred into a suitable type of pharmaceutical homogenizer of the shape of cube or bulb, magnesium stearate in the amount of 2.01% by weight is added and agitated until homogeneous.

The obtained mixture is tableted in rotary tableting machines of the type such as Manesty, Kilian, Fette etc. into smooth, flat tablets with dividing groove.

Tablet parameters:

Appearance	White to off-white, smooth, flat with dividing groove
Tablet diameter (mm)	13
Tablet height (mm)	4.88
Tablet average weight (g)	0.745
Tablet break resistance (N)	70-90

Dissolution of the active ingredient according to this invention as a function of time and its comparison with the product according to EP 0 624 366 A1:

Apparatus Pharmatest type PTWS 3:

Dissolution medium Water (Temperature 37 °, volume 600 ml, 100 rpm)	Time			
	Amount of released active ingredient, %			
	after 1 hour	after 3 hours	after 5 hours	after 8 hours
Tramadol 200-SL	33.48	56.53	69.82	82.7
Tramal ® Retard 200	35.60	66.50	83.90	95.8

Example 5

a) pharmaceutical composition, containing in 1 tablet:

Tramadol hydrochloride	0.2000 g	21.74 %
Glyceryl ester of docosanoic acid	0.3400 g	36.96 %
Calcium phosphate dihydrate	0.3540 g	38.48 %
Polyvinylpyrrolidone	0.0140 g	1.52 %
Colloidal silica	0.0120 g	1.30 %

b) process for its preparation:

The active ingredient in admixture with micronized ester of glycerol with docosanoic acid having the particle size of from 1.5 – 60 micrometers in the amount of 36.9 % by weight is agitated in a suitable type of pharmaceutical granulator such as Diosna, along with calcium phosphate dihydrate in the amount of 38.48 % by weight, for 3 minutes.

Then the mixture is, under constant agitation, moistened with a solution of non-ionic vinylpyrrolidone polymer having the relative molecular weight of 25,000 in the amount of 1.52 % by weight in 60% ethanol.

The mixture is agitated, agglomerate thus being formed.

The prepared agglomerate is discharged from the granulator into the vessel of a fluidising drying device such as Glatt or Aeromatic and is dried at the temperature of fed air 55 °C until the temperature of the effluent air reaches 42 °C. At that point the product reaches residual moisture from 0.5 % to 1.2 %.

The particle size of the dried agglomerate is adjusted by passing through a screen having the mesh side of 1.25 mm on an oscillating device such as Frewitt. The adjusted agglomerate is transferred into a suitable type of pharmaceutical

homogenizer of the shape of cube or bulb, colloidal silica in the amount of 1.30% by weight is added and agitated until homogeneous.

The obtained mixture is tabletted in rotary tableting machines of the type such as Manesty, Kilian, Fette etc. into flat, oblong tablets with dividing groove.

Tablet parameters:

Appearance	Off-white, smooth, oblong with dividing groove
Tablet diameter (mm)	18
Tablet height (mm)	6.6
Tablet average weight (g)	0.920
Tablet break resistance (N)	70-90

Dissolution of the active ingredient according to this invention as a function of time and its comparison with the product according to EP 0 624 366 A1:

Apparatus Pharmatest type PTWS 3:

Dissolution medium Water (Temperature 37 °, volume 600 ml, 100 rpm)	Time			
	Amount of released active ingredient, %			
	after 1 hour	after 3 hours	after 5 hours	after 8 hours
Tramadol 200-SL	30.70	53.40	66.50	79.60
Tramal ® Retard 200	35.60	66.50	83.90	95.8

Industrial Applicability

The invention can be employed in the pharmaceutical industry in obtaining controlled release therapeutic preparations, containing tramadol hydrochloride. Said preparations are indicated in therapy of acute and chronic moderate to strong pain of various origins, in particular in surgery, obstetrics, oncology, rheumatology, orthopaedics, after stomatological operations, in neurology and other fields. It is

useful also for pain in ischaemic diseases (such as in myocardial infarction and in leg ischaemias).

CLAIMS

1. A controlled release pharmaceutical composition containing tramadol hydrochloride characterized in that it contains 100 to 200 mg of the active ingredient in admixture with micronized esters of glycerol with higher fatty acids, alkali salts of phosphoric acid, non-ionic vinylpyrrolidone polymers, substances from the group of salts of higher fatty acids with alkaline earth metals and silicon oxides.
2. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claim 1 characterized in that it contains micronized esters of glycerol with higher fatty acids, preferably the glyceryl ester of docosanoic acid.
3. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claim 2 characterized in that 90 % of the particle size of the docosanoic acid glyceryl ester ranges from 1.5 to 60 micrometers.
4. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claims 2 and 3 characterized in that the contents of the higher fatty acids glyceryl esters is in the range of from 10 to 53 % by weight, preferably from 28 to 47 % by weight.
5. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claims 1 and 2 characterized in that it contains alkali salts of phosphoric acid, preferably calcium phosphate dihydrate in an amount from 20 to 41 % by weight.
6. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claim 5 characterized in that it contains calcium phosphate dihydrate preferably in an amount from 24 to 39 % by weight.
7. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claims 1, 2 and 5 characterized in that it

contains non-ionic vinylpyrrolidone polymers having a relative molecular weight of 9000 to 90,000 in an amount of 1.15 to 1.75 % by weight.

8. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claim 7 characterized in that it contains non-ionic vinylpyrrolidone polymers having a relative molecular weight of preferably 25,000 to 30,000 in amount of preferably from 1.3 to 1.55 % by weight.
9. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claims 1, 2, 5 and 7 characterized in that it contains substances from the group salts of higher fatty acids with alkaline earth metals in an amount of 1.5 to 3.2 % by weight.
10. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claim 9 characterized in that it contains substances from the group salts of higher fatty acids with alkaline earth metals, preferably magnesium stearate in an amount of preferably from 1.8 to 2.8 % by weight.
11. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claims 1, 2, 5, 7 and 9 characterized in that it contains silicon oxides in an amount of 1 to 3.0 % by weight.
12. The controlled release pharmaceutical composition containing tramadol hydrochloride according to claim 11 characterized in that it contains silicon oxides, preferably colloidal silica in an amount of 1.1 to 2.1 % by weight.
13. A method of preparing the pharmaceutical composition according to claims 1 to 12 characterized in that the active ingredient is agitated in admixture with micronized esters of glycerol with higher fatty acids and alkali salts of phosphoric acid wherein said admixture is moisturized with a solution of a non-ionic vinylpyrrolidone polymer in a mixture of water and ethyl alcohol and the mixture is agglomerated.
14. The method of preparing the pharmaceutical composition according to claim 13 characterized in that the active ingredient is agitated in admixture

with micronized esters of glycerol with higher fatty acids, preferably glyceryl ester of docosanoic acid of a particle size from 1 to 100 μm , preferably 1.5 to 60 μm , in an amount of 10 to 53 % by weight, preferably 28 to 47 % by weight, along with alkali salts of phosphoric acid, preferably calcium phosphate dihydrate, in an amount of 20 to 41 % by weight, preferably of 24 to 39 % by weight.

15. The method of preparing the pharmaceutical composition according to claims 13 and 14 characterized in that the mixture of the active ingredient, esters of glycerol with higher fatty acids and alkali salts of phosphoric acid is moisturized with a solution of a non-ionic vinylpyrrolidone polymer of a relative molecular weight from 9000 to 90,000, preferably 25,000 to 30,000, in an amount of 1.15 to 1.75 % by weight, preferably 1.3 to 1.55 % by weight.
16. The method of preparing the pharmaceutical composition according to claims 13 to 15 characterized in that the mixture of the active ingredient, esters of glycerol with higher fatty acids and alkali salts of phosphoric acid is moisturized with a solution of a non-ionic vinylpyrrolidone polymer in a mixture of water and ethyl alcohol in an amount of 30 to 70 % by weight, preferably 40 to 60 % by weight.
17. The method of preparing the pharmaceutical composition according to claims 13 to 16 characterized in that the mixture is agitated and agglomerated, the obtained agglomerate being dried in a suitable manner by fluidising drying, chamber drying or vacuum drying such that the mixture contains from 0.2 to 1.5, preferably from 0.5 to 1.2 % moisture.
18. The method of preparing the pharmaceutical composition according to claims 13 to 17 characterized in that the dried agglomerate is adjusted to a particle size convenient for tableting process and substances from the group of salts of higher fatty acids with alkaline earth metals and/or silicon oxides are admixed, the mixture being agitated until homogeneous.
19. The method of preparing the pharmaceutical composition according to claim 18 characterized in that the dried agglomerate is adjusted to a

particle size convenient for tableting process and admixed are substances from the group of salts of higher fatty acids with alkaline earth metals, preferably magnesium stearate in an amount of 1.5 to 3.2 % by weight, preferably 1.8 to 2.8 % by weight, and/or silicon oxides, preferably colloidal silica in an amount from 1 to 3 % by weight, preferably from 1.1 to 2.1 % by weight.

20. The method of preparing the pharmaceutical composition according to claims 13 to 19 characterized in that the prepared mixture is tableted to tablets having a lenticular, flat oblong or other shapes such that break resistance of the tablets ranges between 40 and 110 N, preferably from 50 to 90 N.



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(54) Title: CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING TRAMADOL HYDROCHLORIDE

(57) Abstract: The invention solves a controlled release pharmaceutical composition containing tramadol hydrochloride, characterized in that it contains 100 to 200 mg of the active ingredient in admixture with micronized esters of glycerol with higher fatty acids, alkali salts of phosphoric acid, non-ionic vinylpyrrolidone polymers, substances from the group of salts of higher fatty acids with alkaline earth metals and silicon oxides and a method for the preparation of this composition.

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/SK 00/00027

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K31/315

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 601 842 A (BARTHOLOMAEUS JOHANNES H A) 11 February 1997 (1997-02-11) column 1, line 9 - line 22 column 2, line 34 - line 56 column 3, line 8 - line 20 column 3, line 41 - line 48; claim 1; examples 1,2 --- -/--	1-20

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *&* document member of the same patent family

Date of the actual completion of the international search

16 July 2001

Date of mailing of the international search report

24/07/2001

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/SK 00/00027

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 98 14176 A (BARTHELEMY PHILIPPE ; FARAH NABIL (FR); GATEFFOSSE S A (FR); JOACHI) 9 April 1998 (1998-04-09) page 1, line 6 - line 11 page 3, line 1 - line 24 page 5, line 15 - line 16 page 7, line 14 - line 24 page 7, line 33 - last line page 8, line 6 - line 16 page 8, line 21 - line 27; claims 1,15,17-19; examples 1,4-6</p>	1-20
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OBAIDAT, AIDAN A.: "Evaluation of the mechanism of release of a water soluble drug from a waxy inert matrix" retrieved from STN Database accession no. 133:125074 XP000990961 abstract page 199, left-hand column, last paragraph -page 199, right-hand column, paragraph 1 page 199, right-hand column, last paragraph -page 200, left-hand column, paragraph 1 & ACTA PHARM. TURC. (1999), 41(4), 199-202 ,</p>	1-20
T	<p>EP 1 020 183 A (GRUENENTHAL GMBH) 19 July 2000 (2000-07-19) page 2, paragraph 1 - paragraph 2 page 2, paragraph 6 - paragraph 9 page 2, paragraph 12 - paragraph 13 page 2, paragraph 15 -page 3, paragraph 17 page 3, paragraph 26 page 4, paragraph 31; claims 1,3-7,9; example 4</p>	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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